

## **Myelin oligodendrocyte glycoprotein and Aquaporin-4 antibodies are highly specific in children with acquired demyelinating syndromes**

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## Abstract

**Aims:** Our objectives were to evaluate the utility of measuring MOG and AQP4 antibodies (Ab) in clinical practice and describe their associated neurological phenotypes in children.

**Methods:** Between 2012-2017, 371 children with suspected acquired demyelinating syndromes (ADS) seen in 3 tertiary centres were tested for MOG-Ab and AQP4-Ab. Medical notes were retrospectively reviewed and clinical and demographic data compiled. **Clinical phenotyping was performed blinded to the antibody results**

**Results:** Following review, 237 of the 371 were diagnosed with ADS. Of these, 76/237(32.1%) were MOG-Ab positive and 14/237(5.9%) were AQP4-Ab positive. None were positive for both autoantibodies. All 134 patients with non-ADS were negative for MOG-Ab. MOG-Ab were identified in 45/70(64.3%) of patients presenting with acute disseminated encephalomyelitis (ADEM) and in 24/25 (96%) of patients with relapsing ADEM. 36/75(48%) MOG-Ab positive patients relapsed. Of the 33 children with neuromyelitis optic spectrum disorder: 14(42.4%) were AQP4-Ab positive, 13(39.4%) were MOG-Ab positive and 6(18.2%) were seronegative. Of the children with longitudinal samples, 8/13(61.5%) AQP4-Ab remained positive during the disease course compared to 35/43(81.4%) MOG-Ab (13/16 monophasic and 22/27 relapsing).

**Conclusion:** MOG-Ab were identified in a third of children with ADS. Almost half of the MOG-Ab positive children relapsed and the majority of them remained antibody positive over 4years follow-up.

Key points from this paper:

1. MOG-Ab is highly specific for acquired demyelinating syndromes and is not identified in children with peripheral demyelination or genetic leukodystrophies/hypomyelination.
2. Up to 48% of MOG-Ab ADS paediatric patients relapse, higher than previously thought.
3. Seroconversion to MOG-Ab negative status is infrequent and therefore patients may be tested MOG-Ab positive at interval sampling even when asymptomatic.
4. **MOG-Ab status should only be used in conjunction with the clinical information to guide maintenance therapy.**

## **Introduction**

The association of Aquaporin-4 (AQP4) and Myelin oligodendrocyte glycoprotein (MOG) antibodies with specific acquired demyelination syndromes (ADS) is now well established. The identification of AQP4-Ab in neuromyelitis optica spectrum disorder (NMOSD)<sup>1</sup> has improved the diagnosis and led to more rapid initiation of treatment. The most recent criteria for the diagnosis of NMOSD stratifies patients according to the presence or absence of AQP4-Ab<sup>2</sup>. Two studies looking at the prevalence of AQP4-Ab in paediatric patients presenting with a first episode of demyelination have identified these in only 0.7% (2/279)<sup>3</sup> to 4.5% (3/64)<sup>4</sup> of children, which may reflect the rarity of NMOSD in certain populations. A recent nationwide study of Japanese children identified AQP4-Ab in 1/12(8.3%) patients with multiple sclerosis (MS) and 3/6(50%) patients with NMOSD patients who were tested<sup>5</sup>. Nevertheless, the severity of NMOSD and the role for specific therapies prompts testing for AQP4-Ab in all children with ADS.

More recently, MOG-Ab have been reported in about 40%<sup>6</sup> of children at first presentation of an acquired demyelinating syndrome, with two studies from the UK/France<sup>7</sup> and the Netherlands<sup>8</sup> suggesting that MOG-Ab identified at onset are associated with a non-MS disease course. Although initially reported in predominantly monophasic disease, MOG-Ab have been detected in patients with multiphasic disseminated encephalomyelitis (MDEM)<sup>9</sup>, recurrent optic neuritis (RON)<sup>10</sup>, and ADEM-ON<sup>11</sup> (acute disseminated encephalomyelitis (ADEM) followed by recurrent or monophasic optic neuritis (ON)), and in both adults and children<sup>12</sup> with NMOSD without AQP4-Ab. Two recent reports identified MOG-Ab and AQP4-Ab in 28/35 (80%)<sup>13</sup> and 34/48(70.1%)<sup>14</sup> of children with non-MS relapsing demyelination.

Both MOG and AQP4 antibodies have been routinely requested in all children with ADS in our centres. In view of the overlap at presentation with other non-ADS neurological syndromes, these antibodies were also requested for patients with a range of non-ADS neurological syndromes. Our primary objective was to establish the clinical relevance of these antibodies with the secondary aim to explore the clinical phenotypes associated with AQP4 and MOG antibodies in an unselected cohort of children with ADS.

## **Methods**

Between 2012-2017, 371 serum samples were sent from Evelina Children's Hospital (92), Great Ormond Street Children's Hospital (192), and Birmingham Children's Hospital (87) for MOG-Ab and AQP4-Ab testing. Patients were identified from the respective pathology department databases. All patients were tested clinically, but not always at the time of first presentation. Patients had undergone brain and spinal cord MRI scans according to local MRI protocols. The clinical data comprising demographic information, clinical features at presentation, discharge and follow up, and results of laboratory testing and neuroimaging were compiled (SD, TR) and presented to two paediatric neurologists (SW, YH) who were blinded to the antibody results. They classified the patients according to established criteria<sup>15</sup> to either ADS or non-ADS aetiology.

Within the ADS group patients were further classified (based on the neurological examination and without reference to neuroimaging features) as optic neuritis (ON), transverse myelitis (TM), polyfocal neurological deficits associated with encephalopathy (ADEM), or polyfocal deficits without encephalopathy.

Relapsing cases were assigned the following diagnostic categories:

1. MS, fulfilling the 2013 International Pediatric Multiple Sclerosis Study Group (IPMSSG) consensus criteria<sup>1</sup> and the 2010 revised McDonald criteria<sup>5</sup>
2. NMOSD, fulfilling the 2015 Wingerchuk criteria<sup>9</sup>.
3. MDEM and ADEM-ON fulfilling the 2013 IPMSSG consensus criteria<sup>1</sup>.
4. Recurrent demyelination in a single CNS area without evidence of clinically-silent disease (for example relapsing ON).

Serum AQP4-Ab and MOG-Ab were tested as part of the routine clinical assessment of children with demyelinating diseases. Serum was sent to the Clinical Neuroimmunology service at the Oxford Radcliffe Hospital Trust, where AQP4-Ab and MOG-Ab were tested using live cell-based assays, as previously described<sup>7</sup>.  
<sup>16</sup>. No CSF samples were available from these children for further analysis.

In order to evaluate if patients with monophasic disease are more likely to have transiently elevated levels of autoantibodies, as previously reported<sup>17</sup>, we additionally report children who had a sample taken acutely and a repeat sample at 3-6months follow-up. Results were assigned into positive and negative diagnostic categories as reported by the reference laboratory.

#### *Statistical analysis*

Statistical analysis was performed using the commercially available software GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA). Nonparametric statistical tests (Mann–Whitney tests) were used for continuous distributions and Fisher exact tests for nominal data. We used the clinical diagnosis at last follow-up, of true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) and used them to determine the following: (1) Sensitivity: the probability of the test finding disease among those who have the disease  $[TP/(TP+ FN)]$ . (2) Specificity: the probability of the test finding no disease among those who do not have the disease  $[TN/(TN+ FP)]$ .

#### *Ethical approval*

As the data analysis was retrospective and no additional data were collected beyond that required for standard medical care of the patient, a full ethics review under the terms of the Governance Arrangements of Research Ethics Committees in the UK was deemed not necessary by the study team and the study was registered as an audit at the respective sites.

## Results

The clinical records for each patient were examined and the diagnoses established. The results are shown in figure 1 and summarised in table 1.

Of the 371 children for whom antibody testing was requested, 237 (63.9%) children were diagnosed with ADS: 117 (49.4%) were monophasic and 120 (50.6%) were relapsing. Overall, 90 (38%) of the 237 patients in the ADS group had antibodies to either MOG or AQP4 compared to 2 in the non-ADS group ( $p < 0.0001$ , Fishers exact). MOG-Ab were identified in 76 patients (32.2%), all with ADS. AQP4-Ab were identified in 16 cases, 14 patients with neuromyelitis optica spectrum disorder (NMOSD) and 2 with systemic lupus erythematosus (SLE) and no evidence of CNS demyelination (both currently on maintenance immunosuppression for SLE). MOG-Ab had 100% specificity (95% CI: 97.28% to 100.00%) and 100% positive predictive value for ADS, with 32.2% sensitivity (95% CI: 26.29% to 38.57%). AQP4-Ab has a 99.4% specificity (95% CI: 97.87% to 99.93%) for NMOSD and a 42.42% sensitivity (95% CI 25.48% to 60.78%). Of the 33 children with NMOSD; 14(42.4%) were AQP4-Ab positive, 13(39.4%) were MOG-Ab positive and 6 were seronegative. All 54 patients with relapsing remitting multiple sclerosis were negative to both autoantibodies. Of note, of the relapsing non-MS phenotypes, 76.5% (52/68) were antibody positive. Of the non-MS ADS, clinical relapses were reported in all patients with AQP4-Ab, 38/76(50%) of children with MOG-Ab and 14/80 (17.5%) of seronegative ADS (Figure 1).

### ***MOG and AQP4 antibodies across the different ADS***

A summary of the results is illustrated in **Figure 1**.

MOG-Ab were detected in 45/70 (64.3%) of the patients presenting with ADEM. Relapse following ADEM was observed in 25/70. The final diagnoses were MDEM (n=16), NMOSD (n=6), and ADEM-ON (n=3). Of the relapsing ADEM patients, 24/25(96%) had MOG-Ab.

Of the 65 patients presenting with optic neuritis (ON), 28/65(43.1%) had MOG-Ab and 2(3.1%) had AQP4-Ab. Twelve patients were diagnosed with MS. Of the 24 non-MS relapsing patients (diagnosed with NMOSD and relapsing ON), 12 had MOG-Ab and 2 AQP4-Ab.

There were 50 patients who presented with transverse myelitis. 36/50 (72%) had a monophasic disease. MOG-Ab was only identified in 3/50(6%, all monophasic). Of the 14 patients who relapsed, 3 were diagnosed with relapsing remitting multiple sclerosis (RRMS) and 8(73%) had AQP4-Ab. These 8 patients were subsequently diagnosed with NMOSD.

Fifty-one patients presented with clinically isolated syndrome. RRMS was the most frequent diagnosis in 38/51(74.5%) of these patients. Four went on to be diagnosed with NMOSD, all of whom presented initially with brainstem syndrome and were AQP4-Ab positive.

### **Serial measurements of antibodies**

Of the 14 patients with AQP4-Ab NMOSD, serial samples were available for 13 patients with a median of 5 samples per patient (IQR 2.5-11). Median follow-up time from first antibody testing was 50.5 months (range 7-106 months). Eight (61%) patients remained seropositive throughout follow up. The remaining 5 patients' seropositivity fluctuated to negative but returned to positive with relapses.

A total of 43 MOG-Ab positive patients had longitudinal testing over the disease course. Of these, 16 patients were monophasic and 27 relapsing. There was a trend to a longer follow-up time in patients with relapsing disease compared to monophasic disease (median 48 months, IQR 31-64 versus median of 36 months, IQR 21-54,  $p=0.17$ )

Of the 16 children with MOG-Ab monophasic ADS (median 2 samples, range 2-4) 13 (81.3%) patients remained seropositive throughout the follow up period. Patients with monophasic illness stayed MOG-Ab positive throughout the follow-up, for a median of 9 months (range 6-51 months) despite not relapsing. Of the 27 children with MOG-Ab relapsing ADS (median 3 samples, range 2-15), 22/27(81.5%) remained MOG-Ab positive. **Two children with relapsing ADEM became seronegative in between attack.** None of the children were MOG-Ab negative at time of relapse of ADS. Persistent levels at 6 months were seen in both monophasic and relapsing patients (11/14 vs 10/13,  $p=1.0$ ).

### **Discussion**

In this large cohort of 371 children who underwent AQP4-Ab and MOG-Ab testing, we demonstrated that both antibodies are clinically relevant in ADS. The testing of 135 non-ADS cases, which included patients with a range of neurological disorders including peripheral neuropathies and neurodegenerative disorders such as leukodystrophies, has allowed us to demonstrate that the current MOG-Ab assay, used clinically, is both sensitive and specific to ADS. Our results were strikingly similar to an Austrian/German cohort identifying MOG-Ab in 65/ 210 (31%) of children with ADS<sup>13</sup>. Similar to the results identified here, relapses occurred in children who become seronegative (reconversion to positive); and there were children who remained relapse free despite very persistently raised antibody titres. **A direct comparison with a previous report of transient MOG-Ab positivity in patients with monophasic ADEM is difficult as a different cut off for positivity than the assay used here, was used<sup>17</sup>.** Although AQP4-Ab are strongly associated with a relapsing disease in children and adults with NMOSD<sup>18</sup>, at an individual level we did not observe that the antibody positivity could be used to reliably predict the subsequent course of disease. In keeping with other antibody-mediated conditions, such as Myasthenia gravis and Anti-NMDAR encephalitis, the data reported here suggest that antibody titres cannot be used in isolation to guide maintenance therapy. Identification of patients who were tested MOG-Ab negative in between clinical events highlight the need for repeat testing when the child is symptomatic if the clinical phenotype is suggestive of MOG-Ab associated disease.

The two patients with AQP4-Ab who did not fulfil diagnostic criteria for NMOSD<sup>2</sup> had an underlying diagnosis of SLE with CNS involvement, without evidence of demyelination. Although it is possible that the positive results may simply reflect false positivity, the association between AQP4-Ab NMOSD and SLE is well described and is thought to represent shared genetic susceptibility to autoimmune disease<sup>19, 20</sup>. AQP4-Abs have previously been reported in a small percentage of patients with non-CNS SLE without concurrent clinical or radiological signs of demyelination and the antibodies have been shown to persist for many years without causing demyelinating disease<sup>21</sup>. It will be important to observe if the two patients in our cohort develop demyelination in the future as previously reported with patients with myasthenia gravis who despite being positive for AQP4-Ab did not present with NMOSD for over 10 years<sup>22</sup>. None of the patients were double positive for both MOG and AQP4 antibodies and all children with MS were negative for both autoantibodies.

Limitations of our study include its retrospective design. A prospective study would have allowed us to standardise the data collection and timing of samples across the different sites. We did not control for treatment effect on antibody levels. Furthermore, a proportion of the patients were only diagnosed at the time of relapse so the antibody results were not available at disease onset. As the aim of this study was to look at the clinical utility of the test, we have categorised the antibody results into positive and negative (as reported clinically) and have not evaluated if fluctuation in antibody titres during the disease course is important. The relationship between MOG-Ab titres and clinical disease activity, however, remains an area of active investigation, with a recent report suggesting that a high MOG-Ab titre ( $\geq 1:1,280$ ) predicted a recurrent non-MS course with a sensitivity of 46% and a specificity of 86%<sup>15</sup>. The utility and applicability of this remains to be evaluated clinically in light of challenges of measuring antibody titres beyond a research setting. Additionally, we did not evaluate the clinical utility of CSF antibody results; one publication has suggested that CSF antibody titres may correlate better than serum in AQP4-Ab NMOSD<sup>23</sup>.

In conclusion, AQP4-Ab were found in children with NMOSD but also in children with SLE who do not have any clinical or radiological features of NMOSD. MOG-Ab were identified in a third of children with ADS but not in children with non-ADS or MS. Half the children with MOG-Ab relapsed, a higher rate of relapsing disease than previously reported by us<sup>7</sup> and others<sup>24</sup>. This is likely to be due to a longer follow-up time and increased awareness of this phenotype amongst patients previously labelled as multiple sclerosis. The identification of MOG-Ab in a range of ADS that relapse raises important questions about management. We recently reported a multinational experience of children with relapsing ADS associated with MOG-Ab associated disease accounting for 23.6% of all relapsing ADS. However, the inability currently to predict the probability of relapse and the prolonged intervals between first presentation and relapse, and interattack intervals -in some cases up to 10 years – mandates the careful management of each case individually.

Table 1: Non-ADS diagnoses

Non-ADS diagnosis	N (%)	Seronegative (n=132)	AQP4-Ab (n=2)	MOG-Ab (n=0)
Acute necrotising encephalopathy of childhood	3 (2%)	3	0	0
Autoimmune encephalitis*	9 (7%)	9	0	0
Cerebellitis	5 (4%)	5	0	0
CNS neoplasm	2 (2%)	2	0	0
Congenital CNS malformation	2 (2%)	2	0	0
Cranial neuropathy	7 (5%)	7	0	0
Encephalitis	5 (4%)	5	0	0
Headaches	6 (5%)	6	0	0
Neurometabolic/genetic disease	4 (3%)	4	0	0
Neurometabolic/genetic disease effecting white matter	11 (8%)	11	0	0
Neuromuscular disorders	2 (2%)	2	0	0
Non-localising neurological signs	20 (15%)	20	0	0
Non-specific white matter changes	2 (2%)	2	0	0
Ophthalmic disease	4 (3%)	4	0	0
Peripheral neuropathy	12 (9%)	12	0	0
Seizure disorder	6 (5%)	6	0	0
SLE without neurological involvement	4 (3%)	4	0	0
SLE with neurological involvement	8 (6%)	6	2	0
Systemic auto-inflammatory disease	14 (11%)	14	0	0

ADS acquired demyelinating syndromes, CNS central nervous system, SLE Systemic lupus erythematosus.

Defined as per recent diagnostic criteria<sup>25</sup>

**Figure 1:** Flow chart study profile showing the diagnosis at onset and last follow-up. There were no differences in follow-up time for the different phenotypes with median follow-up time of 36months (30-60) for patients with MS, 36months (IQR 22-51) for patients with ADEM, 33months (IQR 21-52) for patients with ON, 44months (IQR 16.8-60) for patients with TM and 27months (IQR 24-37) for patients with CIS. \* All patients with RRMS presenting with TM and 11/12 of the patients presenting with ON had abnormal MRI with >2 typical MS white matter lesions at first presentation

**ADEM** acute disseminated encephalomyelitis, **CIS** clinically isolated syndrome, **ON** optic neuritis, **TM** transverse myelitis, **RDS** relapsing acquired demyelinating syndrome, **RRMS** relapsing remitting multiple sclerosis



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